A multi-parametric investigation of vascular alterations in elderly with hypertension

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Purpose: Hypertension is a major risk factor for stroke, dementia, and cognitive decline (1). This is thought to be mediated by several cerebrovascular mechanisms such as increased arterial stiffness, migration and proliferaion of smooth muscle cells, reduced vessel lumen, and thickening of extracellular matrix. However, in vivo biomarker(s) for these mediators are not well established. Prior work in the literature has suggested that the volume of white matter hyperintensity (WMH) is associated with hypertension. However, WMH represents late-stage damage and is irreversible. Therefore, a more sensitive biomarker is desirable as it may provide an early indicator of vascular dysfunction in the brain. In this report, we conducted a multiparametric investigation of hemodynamic changes in hypertension, including cerebral blood flow (CBF), venous cerebral blood volume (vCBV), venous oxygenation (Yv), and cerebrovascular reactivity (CVR) to CO2.

Methods: PARTICIPANT: A total of 45 elderly participants were recruited from a community based cohort. Exclusion criteria were presence of encephalomalacia on prior DHS brain MRI, or other major neurological, psychiatric diseases, or cancer treatment within the last 5 years. The participants had an age range of 61 to 79 years (mean 67, SD 5; 23 females and 22 males). Blood pressure was measured while the subject was lying on the scanner table before entering the magnet bore. Based on a Systolic Blood Pressure (SBP) threshold of 140 mmHg, one can dichotomize the participants into hypertensive (N=23) and non-hypertensive (N=22) individuals. EXPERIMENT: Three MRI scans were performed on each participant using a 3T system (Philips): *CVR and vCBV* were measured by a simultaneous CO2/O2 procedure (Fig. 1a), in which CVR was characterized by the MR signal response to CO2 inhalation and vCBV was estimated by signal response to O2 inhalation (9.3min). In this procedure, three types of gas mixtures were used for challenge: hypercapnia gas (5% CO_2, 21% O2 and 74% N2), hyperoxia gas (95%O2 and 5% N2) and mixed hyperoxia/hypercapnia gas (95%O2 and 5%CO2). The hypercapnia and hyperoxia breathing paradigms were carefully designed and the peak frequencies are distinguishable in both time and frequency domain (Fig. 1b). During the entire session, end-tidal CO2 and O2 were recorded and BOLD images were continuously acquired. *Whole brain CBF* was measured by phase-contrast (PC) MRI at the feeding arteries of the brain. Four PC-MRI scans, with each scan targeting one specific feeding artery was performed (2). *Venous oxygenation (Yv)* was noninvasively assessed from the superior sagittal sinus (SSS) using T2-relaxationunder-spin-tagging (TRUST) MRI technique (3). The venous blood signals were fitted to a monoexponential function to obtain T2, which was in turn converted to Yv via a calibration plot. DATA ANALYSIS: The data were analyzed with previously established procedures to obtain the corresponding vascular parameters (4). A linear regression analysis was performed to examine the dependence of CBF, Yv, CVR, and vCBV values on age, sex and blood pressure, in which the vascular parameters were assigned as the dependent variable while blood pressure, age and sex were used as the independent variables. A P value of 0.05 or less was considered statistically significant.

Results: *CVR:* We first dichotomized the participants into normotensive and hypertensive groups and examined their CVR maps. Figure 2a shows group averaged CVR maps of the two groups. It is clear that CVR in hypertensive group was significantly lower than that in normotensive group, with quantitative analysis (Fig. 2b) confirming significance (P<0.01). Figure 3a shows a scatter plot between CVR and systolic blood pressure. Regression analysis revealed that CVR decreases with age (P=0.02) and blood pressure (P=0.02), and that females have a lower CVR than males (P<0.01). *vCBV*: No significant effect was observed for age, sex and blood pressure. *CBF and Yv:* The dependence of CBF and Yv on blood pressure was similar. This is consistent with the notion that these two parameters have a strong mechanistic link and that they are strongly correlated (P<0.001) in our data. Scatter plots between CBF and blood pressure and between Yv and blood pressure are displayed in Figures 3b and 3c. Regression analysis revealed that both CBF and Yv increased with systolic blood pressure (P=0.03, P=0.02 respectively). Gender effect was also observed in CBF in that females had a greater CBF than males (P=0.03).

Discussions: Diminished CVR in hypertensive individuals is consistent with previous literature that hypertension causes increased arterial stiffness and thickening of extracellular matrix. Therefore, these vessels have reduced capacity to dilate in response to vasoactive stimuli such as CO2. CBF and Yv, on the other hand, showed a paradoxical increase in hypertensive individuals. One possible reason is that higher perfusion pressure associated with hypertension may provide a greater "driving force", resulting in a higher CBF. Yv then follows the changes in CBF provided that the brain's oxygen metabolic rate is unchanged. vCBV seems to be intact in hypertension, presumably because the veins do not have smooth muscles and their vascular microstructural changes in hypertension are minor compared to arterial vessels.

Conclusions: In summary, the present work revealed the relationship between blood pressure and the brain's vascular markers. CBF and Yv increased with blood pressure while CVR decreased with blood pressure in relatively community dwelling elderly sample. These functional vascular markers may precede structural changes of the brain and cognitive decline or clinical symptoms.

References: 1) Waldstein et al. J Hypertens, 30, 2352 (2012); 2) Liu et al. PLoS One, 9, e95721 (2014); 3) Lu et al. MRM, 60, 357 (2008); 4) Blockley et al, MRM, 65, 1278 (2011);

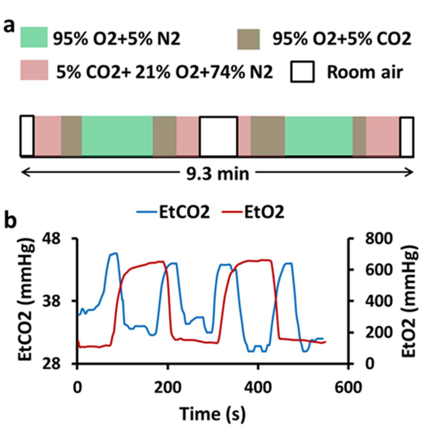

Fig. 1. Simultaneous CO2/O2 breathing challenge. (a) Paradigm design. (b) EtCO2 and EtO2 time courses.

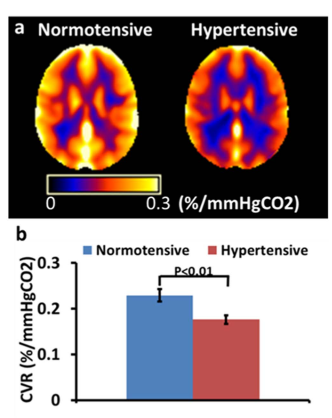

Fig. 2. CVR comparison between normotensive and hypertensive group.

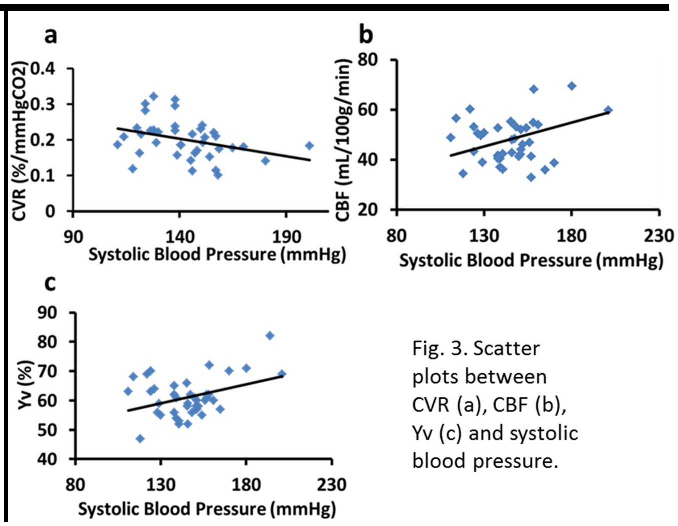

Fig. 3. Scatter plots between CVR (a), CBF (b), Yv (c) and systolic blood pressure.